REMARKS

In the Final Office Action dated October 27, 2008, claims 1-5, 8, 12-13, 22, 29-32 and 36 are pending. Claims 22, 29, 32, and 36 are withdrawn from further consideration. Claims 1-5, 8, 12, and 13 are under examination. Claims 1-5, 8, 12, and 13 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Devalaraja et al., U.S. Patent Application Publication No. 20070059280 (published 15 March 2007, claiming benefit from March 20, 2000), as evidenced by Luross et al., (*Immunology* 2001 Aug. 103(4): 407-416). Claims 1, 5, and 8 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 13 and 14 of co-pending Application No. 10/559,771, in view of Devalaraja et al. (the '280 publication). The objection to the specification is also maintained allegedly because the last paragraph of page 32 is illegible.

This Response addresses each of the Examiner's objections and rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration is therefore respectfully requested.

Objection to the Specification

The Examiner has maintained the objection to the disclosure because the last paragraph of page 32 is illegible.

In response, Applicants have replaced the allegedly illegible paragraph with legible text by way of the foregoing amendments to the specification, as requested by the Examiner. Withdrawal of the objection to the specification is therefore respectfully requested.

Non-statutory Double Patenting

Claims 1, 5, and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 13 and 14 of co-pending Application No. 10/559,771, in view of Devalaraja et al. (the '280 publication).

Applicants observe that Serial No. 10/559,771 is entitled "ELEVATOR WITH A CABLE-DRIVEN CAR", and is not related in any way to the present application. Therefore, it is respectfully submitted that the rejection is in error and withdrawal thereof is respectfully requested.

35 U.S.C. §102(e)

The Examiner has maintained the rejection of claims 1-5, 8, 12, and 13 under 35 U.S.C. §102(e) as allegedly anticipated by Devalaraja et al., U.S. Patent Application Publication No. 20070059280 (published 15 March 2007, claiming benefit from March 20, 2000) ("the '280 publication"), as evidenced by Luross et al., (*Immunology* 2001 Aug. 103(4): 407-416).

The Examiner alleges that the '280 publication teaches a method of treating inflammation or an autoimmune disease by administering to a mammal in need thereof, a therapeutically effective amount of an inhibitor of a G-CSF, which inhibits inflammation or autoimmune disease. The '280 publication also allegedly teaches that inhibitors of G-CSF and G-CSFR include antibodies.

To anticipate the presently claimed invention, the '280 publication must enable the skilled artisan to practice the claimed invention without undue experimentation. See, e.g., Preemption Devices Inc. v. Minnesota Mining & Mfg. Co., 732 F.2d 903, 906, 221 U.S.P.Q. (BNA) 841, 843 (Fed. Cir. 1984). Applicants respectfully submit that the '280 publication does

not provide an enabling disclosure that would anticipate the claimed invention.

In the first instance, Applicants observe that the alleged therapeutic methods disclosed in the '280 publication are merely based on an observation of the synergistic effect of exogenously added G-CSF on chemokine-mediated inflammation. For example, the '280 publication discloses intradermal recruitment of neutrophils by G-CSF plus IL-8, both injected intradermally (see Figure 5 and paragraph 0129). Additionally, the '280 publication discloses the potentiating effect of G-CSF on IL-8-mediated chemotaxis (see Figures 7 and 8). Again, in these experiments, both G-CSF and IL-8 were added to the assays (see paragraph [0128]). Essentially based solely on such synergistic effect of G-CSF on chemokine-mediated inflammation, and absent any evidence with respect to the role of endogenously produced G-CSF alone in inflammation, the '280 publication "proposed" that administration of an inhibitor of CSF would be "a useful tool" (see paragraph 0134). Applicants respectfully submit that the evidence provided in the '280 publication, showing a positive effect of exogenous G-CSF on a cytokine, simply does not adequately support a therapeutic method of treating a disease based on inhibiting (i.e., negating) endogenous G-CSF.

The Examiner has argued that the role of endogenous G-CSF and its receptor in inflammation *in vivo* was known in the art (referring to Paragraph 0003 in the Background section of the '280 publication), thus the '280 publication does not need to teach what is known in the art. However, Applicants respectfully submit that the discussion in Paragraph 0003 of the '280 publication simply suggests that G-CSF may play some role in inflammation, and does not provide any evidence with respect to the role of endogenously produced G-CSF, alone, in inflammation. In fact, in the same paragraph of the '280 publication it was admitted that "by itself, G-CSF is a relatively weak chemoattractant", suggesting a requirement for simultaneous

actions of G-CSF and another cytokine such as IL-8.

In contrast, the present application demonstrates that G-CSF, alone, has the effect of driving bone marrow leukocyte production during inflammatory diseases, such as rheumatoid arthritis. See, e.g., page 40-41 of the specification. The present application provides, for the first time, direct evidence for a role of endogenously produced G-CSF in promoting inflammation *in vivo*, by using G-CSF gene knockout mice in collagen induced arthritis (see Example 14, page 42 of the present specification), which is the most widely accepted mouse model of this human disease. The present application also provides direct evidence that bone marrow production of myeloid cells is enhanced during arthritis and that this response is markedly reduced in G-CSF gene knockout mice. Moreover, the present application provides direct evidence showing that specific blockade of G-CSF in wild type mice by administration of anti-G-CSF antibodies prior to and after the induction of acute arthritis provides a protective effect against the development and progression of disease. See, e.g., page 45, Example 20, and Figures 14A-D of the present application.

In contrast, the '280 publication does not provide any evidence showing the effect of endogenously produced G-CSF, alone, in promoting inflammation *in vivo*. Further, the '280 publication does not provide any evidence with respect to a therapeutic effect of anti-G-CSF antibodies against the progression of a relevant experimental model of inflammation or arthritis. Therefore, it is respectfully submitted that those skilled in the art would not consider the "proposed" treatment based on administration of an inhibitor of CSF, as disclosed in the '280 publication, to be enabling or even credible.

Applicants further respectfully submit that the Examiner's evaluation of the disclosure of the '280 publication should also take into consideration of the complex nature and relative

unpredictability in the field. In this regard, Applicants note that the company, Abgenix, halted their development of an anti-IL-8 antibody for the treatment of rheumatoid arthritis in early 2002, and halted development of that anti-IL-8 antibody in May 2002. A copy of Keystone et al., *Current Opinion Rheumatology*, 15: 253-258 (2003), is attached (as **Exhibit 1**), which describes that no significant clinical benefit was demonstrated in a phase IIa trial with rheumatoid arthritis subjects using anti-IL-8 mAb. See page 256, right column of Keystone et al. That is, even *direct* antagonism of the chemokine IL-8 by administering an anti-IL8 mAb has not proven to be effective by 2003. It is noted that the suggested approach of the '280 publication that anti-G-CSF be used to inhibit the synergistic effects of G-CSF on IL-8 mediated inflammation, was disclosed when the '280 publication was filed in 2001. In light of the failure of treating rheumatoid arthritis with anti-IL-8 mAb, as reported by Keystone et al. (**Exhibit 1**), the approach proposed in the '280 publication would not have been considered by those skilled in the art as adequate or enabling. In fact, those skilled in the art would have had significant doubt as to whether blocking G-CSF, e.g., by administering an antibody specific for G-CSF, would be beneficial at all for the treatment of inflammatory diseases.

Furthermore, Applicants direct the Examiner's attention to the parent application by Devalaraja et al., Serial No. 09/885,259, which has issued as U.S. Patent No. 7,108,852. The '280 publication is based on a continuation application of the '259 application, and therefore both '259 and '280 applications have the same disclosure. In the disclosure, a number of CSFs are suggested as being of potential interest (G-CSF, M-CSF and GM-CSF). Of these, claims directed to M-CSF were elected for prosecution in the '259 application. The background section of the Devalaraja disclosure suggests that a role for M-CSF in inflammation was known, similarly to the comments Devalaraja makes regarding G-CSF. However, it is noted that claims

relating to methods of treating rheumatoid arthritis by administering an antibody to M-CSF were rejected as not enabled during prosecution of the '259 application; and it was only following submission of data from an animal model by way of a declaration that the enablement rejection was overcome. Likewise, the '280 publication does not provide any substantive teaching, or any animal data, in relation to the use of an antibody to G-CSF to treat rheumatoid arthritis. Therefore, at least on its face, the '280 publication is not enabled, and thus cannot anticipate the presently claimed invention.

Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §102(e) based on the '280 publication is overcome. Withdrawal of the rejection is respectfully requested.

Conclusion

In light of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Encl.: Exhibit 1